REMARKS/ARGUMENTS

With this amendment, claims 11-12, 17-19 and 21 are pending. Claims 1-10, 13-16, 20, and 22-28 are cancelled without prejudice to subsequent revival. For convenience, the Examiner's rejections are addressed in the order presented in a June 9, 2004 Office Action.

I. Status of the claims

Claims 1-10, 13-16, 20, and 22-28 are cancelled without prejudice to subsequent revival. Claim 21 is amended to remove dependence on now cancelled claim 20. These amendments add no new matter.

II. Objections to the specification

The Office Action objected to the use of the trademarked term GENECHIP in the application. In order to expedite prosecution, the term has been correct as suggested by the Office Action.

III. Objections to the claims

Claim 21 was objected to for depending in part from non-elected claim 20. In order to expedite prosecution, claim 21 is now amended to depend from claims 17-19. In view of this amendment, Applicants respectfully request withdrawal of the objection.

IV. Rejections under 35 U.S.C. §101

Claims 10-12, 17-19 and 21 are rejected under 35 U.S.C. §101 because, allegedly, the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility. According to the Office Action, although the application teaches that the claimed Mkinase is involved in the cell cycle, there is no teaching of the effects of Mkinase on the cell cycle.

Applicants respectfully traverse the rejection. The Office Action has not put forth a *prima facie* case in support the assertion of lack of utility of the claimed invention. In addition,

Applicants submit evidence to support the utility originally asserted in the application as filed, *i.e.* Mkinase is useful as a diagnostic for cancer.

A. Standard to Assess Utility

According to MPEP §2107, the Examiner should review the claims and the supporting written description to determine whether the utility requirement under 35 U.S.C. §101 is met. No rejection based on lack of utility should be made if an invention has a well-established utility, *i.e.*, a utility that will be immediately appreciated by one of ordinary skill in the art based on the characteristics of the invention, regardless any such utility has been asserted. Neither should any rejection be made for lack of utility if an applicant has asserted a specific and substantial utility that would be considered credible by one of ordinary skill in the art.

In most cases, an applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. §101. MPEP §2107.02 III A. The Court of Customs and Patent Appeals stated in *In re Langer*:

> As a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement of §101 for the entire claimed subject matter unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope.

In re Langer, 183 USPQ 288, at 297 (CCPA, 1974, emphasis in original). To overcome the presumption of sufficient utility as asserted by an applicant, the Examiner must carry the initial burden to make a *prima facie* showing of lack of utility and provide a sufficient evidentiary basis for the conclusion. In other words, the Examiner "must do more than merely question operability--[he] must set forth factual reasons which would lead one skilled in the art to question objective truth of the statement of operability." *In re Gaubert*, 187 USPQ 664, 666 (CCPA 1975).

MPEP §2107.02 IV further states, a detailed explanation should be given for a utility rejection as to why the claimed invention has no specific and substantial asserted utility.

Documentary evidence should be provided when possible. Otherwise the Examiner should specifically explain the scientific basis for his factual conclusions.

B. The Asserted Utility Is Specific and Substantial

The present specification provides, for the first time, the cloning of a nucleic acid that encodes an Mkinase polypeptide. Pending claims are drawn to Mkinase polypeptides, which are also referred to as cell cycle proteins. It is specifically asserted that the Mkinase cell cycle proteins encoded by the claimed nucleic acids are useful to diagnose, treat or prevent cell cycle associated disorders, including cancer. (*See, e.g.*, page 39 lines 18-23 and page 40, line 2 through page 41, line 4 of the specification). The specification also states that the availability of Mkinase amino acid sequences and nucleic acid sequences that encode Mkinase proteins enables assay systems to identify compounds that modulate Mkinase activity, thereby modulating the cell cycle. (*See, e.g.*, page 30 line15 through page 31, lines 15 of the specification). Modulation of uncontrolled tumor growth is specifically asserted at page 31, lines 8-10 of the specification.

Applicants assert that the present invention has a specific utility. Specific utility is defined by the MPEP as a utility that is specific to the subject matter claimed. The MPEP explains that applications show sufficient specific utility when applicants disclose a "specific biological activity" and reasonably correlate that activity to a "disease condition." MPEP §§2107.01 and 2107.02. In the present application, Applicants disclose a "disease condition," *i.e.*, a proliferative disorder, in particular cancer, that correlates with a "biological activity," including kinase activity, ability to affect the cell cycle, modulation of pathways involved in tumor progression, and TRAF protein binding. (*See e.g.*, specification at page 30, lines 6-10 and page 39, lines 22-23.) This application demonstrates that Mkinase cell cycle proteins have associated kinase activity and bind to TRAF4, a protein with a demonstrated role in signal transduction and tumor progression. (*See, e.g.*, specification at page 5, lines 10-23 and page 53, lines 1-2) The application further provides methods for identifying compounds capable of modulating Mkinase cell cycle protein activities, which may be used for treating proliferative diseases, including cancer, and methods to diagnose such diseases by detecting changes in the chromosomal Mkinase gene. (*See, e.g.*, specification at page 30, line 15 through page 31, line

15; page 20, lines 22-27; page 39, lines 20-23; and page 40, line 2 through page 41, line 4.) Applicants thus submit that the present invention has a specific utility, *e.g.*, Mkinase cell cycle proteins and their encoding nucleic acids are, therefore, are targets for development of, for example cancer therapeutics or diagnostics. For example, polymorphisms in the chromosomal Mkinase gene are associated with cancer and can be used to diagnose that disease. These activities are clearly specific for the claimed nucleic acids and not any nucleic acid that encodes a kinase.

Applicants submit Exhibit A, a declaration from Dr. Yasumichi Hitoshi in support of the utility of Mkinase based on the information in the specification, *e.g.*, the cancer diagnostic use of the Mkinase nucleic acid, the ability of Mkinase to bind to TRAF4 and regulate signal transduction related to tumorigenesis, and the kinase activity associated with Mkinase.

Applicants also assert that the present invention has a substantial utility or a "real-world" use. The present invention provides Mkinase cell cycle proteins, demonstrates that Mkinase cell cycle proteins have cell cycle activity, and teaches how to identify modulators of Mkinase cell cycle proteins. Therefore, there is a real-world use of the invention in in the identification of compounds that modulate Mkinase cell cycle proteins and thus are useful as therapeutic agents for treating diseases related to altered cell proliferation, such as cancer.

C. The Examiner Has Not Established A *Prima Facie* Showing of Lack of Utility

The Examiner's rejection of the pending claims for alleged lack of utility was based on the repeated statement that no evidence in the specification or prior art demonstrates a role for Mkinase cell cycle proteins in the cell cycle or an affect of Mkinase on cell proliferation. However, Applicants also asserted the additional utility of using the Mkinase proteins and related nucleic acids as diagnostics and therapeutics for cancer.

Applicants respectfully submit that raising a rejection for lack of utility in such a manner is inconsistent with the proper practice described in the MPEP, which places the initial burden on the Examiner, not Applicants, to provide evidence to support a factual conclusion of the credibility of an asserted utility. In fact, MPEP §2107.02 III.B. specifically cautions Office personnel that, once an assertion of a particular utility is made, "that assertion cannot simply be

dismissed ..... as 'wrong,' even when there may be reason to believe the assertion is not entirely accurate." Instead, the Examiner must provide an explanation setting forth the reasoning used in concluding that the asserted specific and substantial utility is not credible; support for factual findings relied upon in reaching the conclusion; and an evaluation of all relevant evidence of record, including utilities taught in the closest prior art. MPEP §2107.02 IV.

The Examiner provided none of the above. Applicants respectfully submit that a *prima facie* showing of lack of utility is not established and the rejection thus cannot properly stand.

D. The asserted Mkinase cell cycle protein utility of association with cancer is correct.

In support of the utility asserted in the application as filed, Applicants submit as Exhibit B the following published journal article: Kato *et al.* Genomics 79:760-767 (2002). Kato *et al.* disclose a human N-terminal kinase like (NTKL) nucleic acid and encoded protein. Starting with the first encoded methionine of the claimed sequences, the nucleic acid and amino acid sequences of Kato *et al.* share 99% identity with the claimed nucleic acid and amino acid sequences. Thus, the claimed Mkinase proteins and related nucleic acids are substantially the same as the NTKL nucleic acids and encoded proteins.

Kato *et al.* demonstrate that the NTKL gene maps to a chromosome 11 region known to contain breakpoint for chromosome translocations reported in extragonadal germ cell tumors and renal cell carcinomas. (See. *e.g.*, Kato *et al.* at page 762.) Thus, NTKL gene, *i.e.*, the Mkinase gene, is associated with cancer. Kato *et al.* also demonstrate that a related isoform of the NTKL protein localizes to the centrosomes during mitosis, strongly suggesting that NTKL proteins *i.e.*, Mkinase cell cycle proteins, have a role in the cell cycle.

Kato *et al.* reported that the NTKL protein did not have kinase activity. Applicants reassert that Mkinase cell cycle proteins have associated kinase activity that is detectable under specific experimental conditions. (See, *e.g.*, Example 2 at page 52 lines 14-18 and Figure 4.) Applicants also assert that the presence or absence of kinase activity in Mkinase

cell cycle proteins, does not affect the utility of the Mkinase nucleic acids to detect polymorphisms in the genomic Mkinase nucleic acid, thereby diagnosing cancer.

Applicants submit a declaration from Dr. Yasumichi Hitoshi in support of the cancer diagnostic use of Mkinase as disclosed in the specification and confirmed by Kato *et al.*

The Office Action also appears to assert that kinases can have different functions and thus, that Mkinase lacks a well-established utility. In support of this assertion the Office Action cites Cook *et al.* (*Biochem. Soc. Trans.* 28:233-240 (2000)). (Office Action at pages 4-5.) According to the Office Action, the of Mkinase associated kinase activity toward a MAP kinase substrate myelin basic protein does not endow the Mkinase with a utility because MAP kinase can be either a positive or negative regulator of signal transduction pathways. Applicants respectfully submit that an assertion of cancer diagnostic function is sufficient to meet the utility requirement under 35 U.S.C. §101, and that modulators, *e.g.*, inhibitors, of a cell cycle regulator, such as Mkinase or MAP kinase, also have utility. For example, an inhibitor of a protein that enhances cell proliferation is useful for treatment of diseases such as cancer. Similarly, an inhibitor of a negative regulator of the cell proliferation is useful for treatment of hypoproliferative diseases or to promote wound healing. Thus, the asserted utilities for both Mkinase and modulators of Mkinase meet the utility requirement under 35 U.S.C. §101.

In view of the above arguments and evidence, Applicants respectfully assert that the Mkinase cancer diagnostic utility disclosed in the application as filed is correct and request that the rejection under 35 U.S.C. §101 be withdrawn.

V. Rejections under 35 U.S.C. §112, first paragraph, enablement

Claims 10-12, 17-19, and 21 are rejected under 35 U.S.C. §112, first paragraph as allegedly lacking enablement. Specifically, the Office Action alleges that the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility, and that one of skill would not know how the use the claimed invention.

Applicants have submitted arguments and evidence in support of the Mkinase utility asserted in the application as filed in Section IV of this response. In view of those

arguments and evidence, Applicants respectfully request that the rejection under 35 U.S.C. §112, first paragraph also be withdrawn.

Claims 10, 11, 17-19, and 21 are also rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement for proteins that have 95% identity to SEQ ID NO:2. According to the Office Action, the specification does not enable one of skill to make and/or use the invention commensurate in scope with the claims. In particular the Office Action alleges that no biological function of provided for Mkinase proteins. Office Action at page 6. The Office Action also alleges that undue experimentation is required to practice the claimed invention. To the extent the rejection applies to the amended claims, Applicants respectfully traverse the rejection.

The Examiner appears to have focused improperly on inoperative embodiments, leading to the conclusion that undue experimentation would be required to identify Mkinase proteins for use in the claimed invention. However, the proper test of enablement is "whether one skilled in the art could make or use the claimed invention from the disclosure in the patent coupled with information known in the art without undue experimentation" (*see, e.g.*, MPEP §2164.01). In the present application, one of skill would know how to avoid inoperative embodiments and to identify active Mkinase proteins, without undue experimentation (*see, In re Cook and Merigold*, 169 USPQ 299, 301 (C.C.P.A. 1971)). Moreover, the present application provides guidance in the form of assays and working examples for Mkinase binding and kinase activities.

Claims reading on inoperative embodiments are enabled if the skilled artisan understands how to avoid inoperative embodiments. As described by the court in *In re Cook and Merigold*, 169 USPQ 302:

> Many patented claims read on vast numbers of inoperative embodiments in the trivial sense that they can and do omit 'factors which must be presumed to be within the level of ordinary skill in the art'....There is nothing wrong with this so long as it would be obvious to one of ordinary skill in the relevant art how to include those factors in such a manner as to make the embodiment operative rather than inoperative.

See, In re Cook and Merigold, 169 USPQ at 302 (quoting in part *In re Skrivan*, 166 USPQ 85, 88 (C.C.P.A. 1970)).

The claims are directed to 1) Mkinase proteins with at least 95% identity to SEQ ID NO:2 and that bind to TRAF4, 2) methods of identifying bioactive agents that bind to the Mkinase protein, and 3) methods of identifying bioactive agents that interfere with Mkinase binding to TRAF4.

The Examiner appears concerned that if one of skill in the art chose to change the amino acid sequence of the recited Mkinase proteins, the skilled artisan would likely choose to make an inoperative embodiment. The Examiner's concern is misplaced for the following reasons. The properties of amino acids are well known to those of skill in the art. Amino acids are characterized by their hydrophobicity, charge, and bulk of side chains, for example. Knowing the properties of particular amino acids, the skilled artisan could easily choose appropriate amino acids to change in a Mkinase enzyme and could avoid adding amino acids that would be detrimental to the structure or function of the polypeptide. The specification also discloses regions of the Mkinase protein structure that correlate with function. For example, the kinase domain is identified in Figure 7 by comparison to known kinase proteins. Based on Figure 7, those of skill would be able to identify conserved residues in the kinase domain whose alteration could have a detrimental effect on kinase activity. (*See also* Example 5.) Figure 5 demonstrates that Mkinase proteins with an N-terminal deletion retain kinase activity and also identifies a nuclear localization signal at the C-terminus of the protein. (*See also* Example 2.)

Factors such as the amount of guidance presented in the specification and the presence of working examples must be considered to determine whether undue experimentation is required to practice the claimed invention (*see*, *Ex Parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int. 1985) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988)). As described in *Wands*, "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed" (*see*, *Wands*, USPQ2d at 1404, quoting *In re Jackson*, 217 USPQ 804 (Bd. Pat. App. & Int. 1982)).

At the time of the present invention, identification of proteins having the functional and structural characteristics described above was well within the means of one of skill of the art, without undue experimentation. The present specification provides working examples and discloses standard techniques known to those of skill in the art, for the identification of functional Mkinase having at least about 95% identity to SEQ ID NO:2. For example, one of skill in the art could use standard manual or computer sequence alignment to determine whether potential sequences have the specified identity (*see, e.g.*, specification, pages 6-8).

Moreover, functional assays to identify Mkinase proteins of the invention are known to those of skill in the art and disclosed in the specification. For example, the specification describes methods of Mkinase binding to proteins such as TRAF4 or to assay Mkinase kinase activity (*see, e.g.*, Examples 2 and 5).

Given the disclosure of the specification and the knowledge of those of skill in the art, the claimed invention is fully enabled. Applicants, thus, respectfully request withdrawal of the rejection for alleged lack of enablement.

VI. Rejections under 35 U.S.C. §112, first paragraph, written description

Claims 10, 11, 17-19, and 21 are rejected under 35 U.S.C. §112, first paragraph as allegedly containing subject matter that was not described in specification. The Office Action points out that the purpose of the written description requirement is to demonstrate that the inventors had possession of the claimed invention at the time of filing. The Office Action alleges that the specification teaches the structure of only a single representative species of Mkinase protein, and thus, that the claimed genus of proteins with 95% identity to SEQ ID NO:2 lacks description.

According to the MPEP the written description requirement for a claimed genus can be satisfied by description of a representative number of species through actual reduction to practice or by disclosure of relevant, identifying characteristics common to the members of the genus, *i.e.*, "structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a

combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus . . ." MPEP 2163.II.A.3.a.ii

To the extent the rejection applies to the claims, Applicants respectfully traverse the rejection. The claims are directed to claims are directed to 1) Mkinase proteins with at least 95% identity to SEQ ID NO:2 and that bind to TRAF4, 2) methods of identifying bioactive agents that bind to the Mkinase protein, and 3) methods of identifying bioactive agents that interfere with Mkinase binding to TRAF4. Applicants submit that the specification provides adequate description of the claimed methods and of the Mkinase genus recited in the method claims.

First, the recited polypeptides all share at least 95% identity to a reference sequence, *i.e.*, a structural characteristic of the claimed genus. Those of skill are able to determine percent identity shared by two amino acid sequences, using well known computer programs and web sites for sequence analysis. Moreover, structural domains of the Mkinase are identified in the specification, *e.g.*, kinase domains and nuclear localization domains are shown in Figure 5, and kinase domains are also shown in Figure 7. Second, the recited polypeptides bind to TRAF4. Assays for proteins that bind to Mkinase include two hybrid assays described at page 38, line 3 through page 39, line 2 and at Example 4. Thus the specification adequately describes the claimed invention.

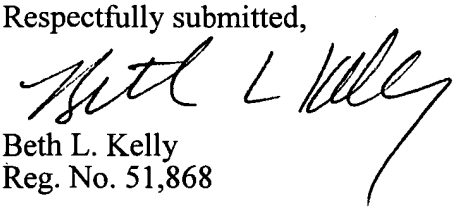
In view of the above amendments and remarks, Applicants respectfully request that the rejection under 35 U.S.C. §112, first paragraph be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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Attachments
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